REMARKS

By the present communication, claims 7-8 and 11-13 are amended, claims 17-22 are new, and claims 2, 5, 6, and 14 are canceled without prejudice. No new matter has been added as the amended claim language is fully supported by the specification and claims as originally filed. Applicants expressly reserve the right to pursue the canceled subject matter in a timely filed continuation application. Claims 1-4, 9-10, and 15-16 are presently withdrawn, and claims 1, 9, 10 and 15-16 are also amended. Applicants note that upon allowance of the product claims, they will be entitled to rejoinder of process claims that depend from or otherwise include all of the elements of the patentable product. In view of the foregoing amendments and the following remarks, Applicants respectfully request reconsideration of this application.

I. Rejections Under 35 U.S.C. § 112, 2nd Paragraph

Claims 7 and 8 were rejected under 35 U.S.C. § 112, 2nd Paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention. Applicants acknowledge that SEQ ID NO: 1 and 2 are identical sequences according to the paper sequence listing and the computer readable format. As described in Table 1 of the specification and recognized by the Examiner, however, Applicants intend "to encompass the NH_2 sequence with SEQ ID NO: 1, and the same sequences except with a biotin-aminohexanoyl instead of a NH_2." Therefore, Claims 7 and 8 have been amended according to the Examiner's suggestions and Applicants respectfully request the rejection be withdrawn.

II. Rejections Under 35 U.S.C. § 112, 1st Paragraph

Claim 14 stands rejected under 35 U.S.C. §112, 1st paragraph as allegedly lacking enablement. Similarly, Claims 5-8 and 11-13 stand rejected under 35 U.S.C. §112, 1st paragraph "because the specification does not reasonably provide enablement for the entire scope of the claimed invention." Office Action, p. 3, paragraph 4. In particular, the following Wands factors are cited against Applicants: claim breadth, the amount of direction provided, nature of the invention, state of the art, and the predictability of the art. *Id.*, Pages 4-8. As claims 5, 6, and 14

have been canceled, the rejections are moot with respect to these claims. Applicants respectfully traverse the remaining rejection of claims 7-8 and 11-13.

Applicants begin by emphasizing that the legal standard for enablement is whether one skilled in the art could make or use the invention without "undue experimentation," and not simply whether "further experimentation" is needed as asserted in the Office Action (see e.g., p. 5, lines 5 and 16). Even complex experimentation is not necessarily undue, if the art typically engages in such experimentation. MPEP §2164.01, citing *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n, 1983). Moreover, as set forth in *Cross v. Iizuka* (753 F.2d 1040, 1050 (Fed. Cir. 1985)) and acknowledged in the MPEP, "a rigorous or invariable exact correlation is not required" between in vitro or in vivo animal model assays and a disclosed or claimed method of use. MPEP, §2164.02, Correlation : *In Vitro/In Vivo*. Based on these standards, which must inform any Wands' factor analysis, it is clear for the reasons that follow that Applicants have enabled the claimed composition of peptides and their use in the treatment of viral infections.

Applicants respectfully submit that the Wands factors for evaluating enablement, discussed in the Office Action on pages 4-8, fully support the enablement of the entire scope of claims 7-8 and 11-13. First, the present claim breadth is reasonable. As amended, Claim 7 recites a composition comprising a very specific genus of related antiviral peptides, each of which includes a membrane transiting sequence motif. Claim 8 and new Claims 20-22 further define peptides of the genus. As shown in Example 2 and as discussed below, representative members of this genus possess significant antiviral activity. In view of the specific peptides claimed, their common relationship—membrane transiting sequence motifs—and the evidence of efficacy and mechanisms of action presented below, it will be clear to the skilled artisan that the claimed subject matter is not unreasonably broad.

Furthermore, Applicants respectfully submit that the nature of the invention, state of the art, and unpredictability thereof have been misapprehended in the Office Action. It is asserted in the Action that "the specification is enabling for an *immunogenic composition* comprising an

antiviral peptide that treats herpes simplex virus (HSV) type 1 ocular disease." Page 3, item 4 (emphasis in original). The rejection also contains an extensive discussion on pages 6-8 on the state of the art as it relates to biologicals, i.e., vaccines, in the treatment of various viral infections, including HIV and HSV. Applicants submit that the person of ordinary skill in the art will readily understand that the claimed invention has nothing to do with the use of membrane transiting peptides as immunogenic compositions or vaccines. The application lacks any discussion of inventive peptides as immunogens or components of vaccines. Instead, all the examples relate to antiviral activity assessed non-immunologically as for other antiviral agents. Indeed, Example 2, FIG. 3, directly compares the antiviral activity of a peptide of the invention to that of the well-known broad spectrum antiviral, acyclovir. In view of the teachings of the specification, it is simply contrary to the understanding of the skilled artisan to assert that the claimed invention recites the use of inventive peptides as immunogens and/or vaccines. As such, the discussion of the state of the art and predictability of immunogens and/or vaccines with regard to HIV and HSV is not relevant to enablement of the claimed compositions and, therefore, fails to support the present rejection.

In contrast, the application presents extensive and detailed in vitro and in vivo data regarding the biological and therapeutic effects of representative peptides from the claimed genus. For example, peptides of the invention show significant antiviral activity against HSV-1 in vitro by blocking plaque formation and lowering viral yield in cell culture (Example 2, FIGS. 1A-1E, 2, and Table 3). At the same time, peptides of the invention showed excellent potential therapeutic index: the antiviral effects of the compounds were obtained at concentrations up to 100-fold lower than cytotoxicity as judged by the trypan-blue exclusion assay (Example 2). The in vitro activity is matched by in vivo activity as demonstrated in Example 9. In the latter example, the corneas of mice were exposed to HSV-1 in the presence and absence of peptides of the invention. As shown in FIGS. 9A and 9B, peptides of the invention significantly inhibited the progression of ocular disease in the mice as judged by vascularization and stromal keratitis over the course of the study. Collectively, these examples provide ample guidance in the use of compositions comprising antiviral peptides of the invention.

Additional experimental evidence submitted herewith supports this contention, showing that the methodology may be applied without substantial experimentation to a broad range of viruses. Applicants formally submit this data herewith via the declaration of Dr. Curtis Brandt (hereinafter, "Brandt Dec."), paragraphs 6-10, Appendix. The Examiner's attention is directed to paragraph 8 of the Brandt declaration and the attached Published U.S. Patent Application US 2005/0203024 (hereinafter, "the '024 application") which is by the same Applicants and which describes the activity of inventive peptides against additional viruses. Example 10 of the '024 application shows that bKLA (SEQ ID NO:5 in the present application) reduced HIV viral titers in a dose-dependent fashion as judged by p24 antigen reduction (see, e.g., FIG 10A). Likewise, Examples 11 and 12 of the '024 application demonstrates that peptides of the invention (SEQ ID NOs:1, 5, 7, 8 and 10) also blocked infection by Influenza A in vitro (FIGS. 11A-D, 12C-D), and Example 12 demonstrates that peptides of the invention exhibit antiviral activity against H5N1 Avian Influenza virus in vitro. In an even more impressive demonstration of activity, peptides of the invention protected mice infected with lethal doses of Influenza Strain PR8 from death as described in Example 13 of the '024 application. Protective effects were observed for delivery of inventive peptides both pre- (FIG. 13) and post-infection (FIG. 14). This latter example directly supports the use of inventive peptides in the treatment and prevention of viral infection.

Still more support for the efficacy of the claimed peptides against viral infections may be found in the data regarding vaccinia infection presented in the Brandt Dec. (para. 7-10, Appendix). Vaccinia virus is a pox family virus and is used in the vaccine for small pox virus. As shown in Dr. Brandt's declaration, the EB peptide (SEQ ID NO: 1) reduced viral titers of vaccinia virus in vitro in a dose-dependent manner (see Para. 9 and Example A of the attachment to Brandt Dec.). Similar results have been obtained with non-enveloped viruses in which the EB and KLA peptides inhibited infection of cells by HPV 31 and the EB peptide and HOM family peptides inhibited infection by Bovine Papillomavirus. Brandt Dec., para. 10, Appendix Examples F and G. Of the many viruses tested, only adenovirus has shown any resistance to peptides of the invention. *Id.* Collectively, the data in the present application, the '024

application, and the Brandt Dec., clearly show that peptides of the invention possess wide ranging anti-viral activity.

Moreover, the present application and the additional data presented herein show that the peptides of the invention, containing membrane transiting sequence motifs, display unique mechanisms of action, unrelated to immunogenicity or vaccines. Examples 4 and 7 of the present application show that antiviral peptides of the invention act early in the viral life cycle of HSV and likely block entry of the virus into the host cell. Similarly, Example 13 of the '024 application (paragraphs 162-164) shows that SEQ ID NOs:10 and 11 selectively block entry of HSV into cells. Although exposure of HSV to a peptide of the invention caused aggregation of the virus (Example 5, present invention), the nature of the increase in peptide IC_{50} with increasing viral concentration is consistent with causation by interaction of the peptide with viral components rather than by virus aggregation. Virucidal effects were seen at higher concentrations of peptide than that needed to bring about the antiviral effects (Example 8, present invention). Additional data regarding the basis of the antiviral activity exhibited by the EB peptide is presented in Examples B, C, D, and E of the attachment to the Brandt Dec. and are consistent with data from examples 4-7 of the present application and Example 13, paragraphs 162-164 of the '024 application. Namely, the predominant antiviral effect of EB appears to involve blocking viral entry through interaction with viral components and is not mediated by the host cell.

In view of the above evidence, the Examiner's reliance on Richards (J. Virol., June 2003, 6692-99) to show the unpredictability of treating or preventing human HSV-1 oral, genital, or ocular disease is misplaced. Richards is concerned with assessing "the potential of therapeutic vaccination of animals latently infected with herpes simplex virus type 1 (HSV-1) to enhance protective immunity to the virus and thereby reduce the incidence and severity of recurrent ocular disease." Richards, Abstract. As noted above, the present invention has nothing to do with vaccines, which are not encompassed by the claims. Antiviral peptides of the present invention exert their effect by blocking viral entry, inactivating the virus, or both. Therefore, Richards

lacks any relevant teachings one way or another regarding the present compositions and cannot provide a basis for rejection of the present claims.

As noted above, an exact correlation between assays and claimed methods is unnecessary, and routine experimentation to, e.g., optimize claimed compositions for use in treating a virus is permissible. Here, the Examiner has not cited any art showing that the skilled artisan would find the present data, especially the in vivo data, to require undue experimentation in the practice of the invention. As noted in the specification on page 8, lines 7-24, each of the viral assays presented in the present application are well-known in the art and are utilized by skilled artisans to determine and demonstrate treatments for viral infection. In fact Brandt et al. 1992 and Brandt et al. 1996 show that agents which are active in the mouse model are typically active in other models of HSV. (Brandt, C.R., Spencer, B., Imesch, P., Garneau, M., Deziel, R. "Evaluation of a Peptidomimetic Ribonucleotide Reductase Inhibitor with a Murine Model of Herpes Simplex Virus Type 1 Ocular Disease" Antimicrobial Agents and Chemotherapy May 1996 p 1078-1084 Vol 40, No. 5 (submitted with IDS, mailed 7/25/2001); Brandt, C.R., Coakley, L.M., and Grau, D.R. "A murine model of herpes simplex virus-induced ocular disease for antiviral drug testing" Journal of Virological Methods Vol 36 1992 P 209-222 (submitted herewith)) Likewise, the data for HIV, Influenza A including H5N1 Avian Influenza, human and bovine papilloma virus and vaccinia, demonstrate the predictability of the antiviral activity of inventive peptides with a wide range of viruses. Hence, Applicants submit that those of skill in the art can use the claimed compositions without substantial experimentation.

Therefore, based on the nature of the invention, the high level of skill in the art (as admitted in the Office Action, page 8, line 14), the state of the art and predictability thereof, and the ample guidance provided Applicants and confirmed by subsequent data, one of skill in the art would not have to engage in undue experimentation to practice the claimed invention. Accordingly, Applicants respectfully request that this ground of rejection be withdrawn.

III. Rejections Under 35 U.S.C. § 102

Claims 1 and Claims 11-13 stand rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by U.S. Patent No. 5,700,780 ("Beaulieu"). Applicants assume the Examiner intended to assert that Beaulieu anticipates Claim 5 and not Claim 1, as Claim 1 has been withdrawn from consideration by Applicant's election without traverse of Group IV, Claims 5-8 and 11-14. Accordingly, the rejection of Claims 5 and 14 over Beaulieu is rendered moot by Applicant's cancellation of Claims 5 and 14. Applicants respectfully traverse the remaining rejections.

Applicant's invention, as defined, e.g., by amended Claim 7, distinguishes from the prior art by teaching a composition comprising an antiviral peptide selected from a specific group of peptides based on membrane transiting peptides that exhibit antiviral activity. The peptides taught by Beaulieu (formula 1) do not encompass the antiviral peptides of Claim 7. Because Claims 11-13 of the present invention have been amended to depend from Claim 7, none may be anticipated by Beaulieu. Moreover, because new Claims 19-22 depend from Claim 7, Applicants submit that the new claims are also patentable over Beaulieu. Applicants respectfully request withdrawal of the rejection of Claims 7, 8, and 11-13.

Applicants respectfully traverse the rejection of Claims 5, 6, 11, and 12 under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 6,635,248 ("Ternynck"). The rejection of Claims 5 and 6 are rendered moot by Applicant's cancellation of these claims. As amended, Claims 11-12 depend from Claim 7, which recites specific sequences of antiviral peptides. Ternynck simply does not teach the antiviral peptides recited by Claim 7 of the present invention. As such, Ternynck can not anticipate claims 11 and 12. Moreover, because new Claims 19-22 depend from Claim 7, Applicants submit that the new claims are also patentable over Ternynck. Applicants respectfully request the withdrawal of this ground of rejection.

IV. Rejoinder and Objections to Claims 7 and 8

As acknowledged in the Office Action dated 6/14/2005, page 2, upon allowance of linking claims, the withdrawn claims will be rejoined. Applicants respectfully submit that linking claims 7 and 11-14 are now in condition for allowance as described above. Rejoinder and allowance of withdrawn subject matter, including claims 1, 3-4, and 9-10 is respectfully requested. As new claims 17-18 depend from claims 1 and 3, respectively, Applicants submit that Claims 17-18 be allowed as well.

Further, as acknowledged in the same paper (page 5), process claims "that depend from or otherwise include all the limitations of the patentable product will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. To that end, applicants have amended process claims 15-16 to recite all of the elements of the appropriate product claims. Rejoinder and allowance of claims 15-16 is respectfully requested.

Finally, Applicants respectfully traverse the objections to claims 7 and 8 as being redundant because the scope of the elected subject matter is deemed the same. Upon rejoinder of the withdrawn subject matter of claims 7-8 as requested above, the scope of claims 7-8 will not be the same. Accordingly, withdrawal of this objection is respectfully requested.

V. Conclusion

For the foregoing reasons, Applicants respectfully submit that the application is now in a condition for allowance. Consequently, Applicants respectfully request the Examiner withdraw all of the rejections and allow the application to issue. The Examiner is invited to contact the undersigned by telephone if a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

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